

REMARKS

Amendments to Claims

Claims 91, 100, 102, 104, 106, 108, 110, 112, 114 and 117 were amended to more clearly define Applicants' claimed invention and to correct inadvertent typographical errors. Support for the claim amendments can be found throughout the specification. For example, page 10, lines 3-6, page 17, lines 4-7 and page 31, lines 1-10 describe the ratio of l-amphetamine to d-amphetamine in the compositions of the invention; and page 30, lines 21-28 and page 93, line 10 through page 97, line 8 describe improvements in the formation of new long-term memory (memory consolidation) following the administration of l-amphetamine.

No new matter has been added to amended Claims 91, 100, 102, 104, 106, 108, 110, 112, 114 and 117. Entry is requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) was filed at the U.S. Patent and Trademark Office on September 5, 2003. Entry of the SIDS is respectfully requested.

Rejection of Claims 91-119 under 35 U.S.C. § 103(a)

Claims 91-119 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gelowitz, *et al.*, *Pharmacology Biochemistry and Behavior* 47:41-45 (1994) (hereinafter "Gelowitz"), Soetens, *et al.*, *Neuroscience Letters* 161:9-12 (1993) (hereinafter "Soetens") and Brown, *et al.*, *Behavioural Brain Research* 114:135-143 (2000) (hereinafter "Brown"). In particular, the Examiner stated that Gelowitz teaches or suggests the use of l-amphetamine in improving cognitive function, namely learning and spatial working memory and that d-amphetamine, known to be more active than l-amphetamine, is associated with adverse side effects which are not associated with l-amphetamine. The Examiner further stated that Soetens teaches or suggests the use of d-amphetamine in enhancing memory consolidation. In addition, the Examiner stated that one of ordinary skill in the art would have expected that l-amphetamine would have the memory consolidation enhancing activity of d-amphetamine, and lack the

tolerance development and physical dependence of d-amphetamine. Further, the Examiner stated that one of ordinary skill in the art would have been motivated to reduce the adverse effects of d-amphetamine.

Applicants have canceled Claim 116.

Applicants' Claims 91-115 and 117-119, as amended, are directed to a method of improving memory consolidation in a human comprising the step of administering an amphetamine to a human having an impairment in memory consolidation, wherein the amphetamine is administered as a component of a composition that includes at least about 90 mole percent l-amphetamine relative to the total amphetamine content of the composition. The amphetamine can be administered to the human as a single dose or in multiple doses. The impairment in memory consolidation in the human can be assessed before, during and after the administration of the amphetamine to the human.

Advantages of Applicants' claimed invention include improvements in memory consolidation without adverse side effects, such as addiction and increases in blood pressure and heart rate.

The standard of patentability to be applied in an obviousness rejection under 35 U.S.C. § 103 is stated in Section 2141 of the Manual of Patent Examining Procedure (MPEP) as follows:

Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquiries enunciated therein as a background for determining obviousness are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the pertinent art;
- and
- (D) Evaluating evidence of secondary considerations.

On page 2100-116 of Section 2141 (February, 2003 edition), the MPEP states the following as basic considerations when applying an obviousness rejection:

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

- (A) The claimed invention must be considered as a whole;
- (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
- (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
- (D) Reasonable expectation of success is the standard with which obviousness is determined.

Gelowitz is directed to the use of chronic (4 months) l-deprenyl or l-amphetamine administration to enhance cognition, in particular, the acquisition of learned spatial habit of rats, as assessed by a modified Morris Water Maze Task. The purpose of Gelowitz was to compare the effects of chronic l-deprenyl with those of l-amphetamine on brain monoamine oxidase activity and on the cognitive performance of middle aged rats in the Morris Water Maze Task. There is no disclosure or suggestion in Gelowitz of a method of improving memory consolidation in a human by administering l-amphetamine, which is the subject matter of Applicants' claimed invention. Specifically, there is no disclosure or suggestion in Gelowitz of using l-amphetamine to improve memory consolidation in a human. The modified Water Maze Task employed by Gelowitz tested the acquisition of learned spatial memory in rats following the administration of l-deprenyl or l-amphetamine.

Applicants enclose with this Reply a Declaration of Randall L. Carpenter, M.D., under 37 C.F.R. § 1.132. Dr. Carpenter is the Chief Executive Officer of Sention, Inc., the assignee of the above-referenced application. Dr. Carpenter states in his Declaration that the modified Morris Water Maze Task employed by Gelowitz, does not specifically assess memory consolidation. Dr. Carpenter further states in his Declaration that the modified Morris Water Maze Task employed by Gelowitz may be assessing drug-induced improvements in motor function and vigor of the rats which would not lead one of ordinary skill in the art to conclude that the improved performance observed by Gelowitz was a consequence of an improvement in memory consolidation.

Therefore, there is no disclosure or suggestion in Gelowitz of a method of improving memory consolidation in a human, comprising administering l-amphetamine to the human, which is the subject matter of Applicants' claimed invention. Additionally, the teachings of Gelowitz would not suggest any reasonable expectation of success in treating a human having an impairment in memory consolidation with l-amphetamine since Gelowitz, on page 43, states:

One of the main metabolites of L-deprenyl is L-amphetamine (15), a compound that is considerably less active than its + isomer D-amphetamine.

(emphasis added).

Soetens describes the effects of d-amphetamine on memory consolidation in humans employing a free recall list of unrelated words. Soetens describes an improvement in the number of words recalled by a human test subject following the administration of d-amphetamine.

Soetens does not remedy the deficiencies of Gelowitz. Specifically, there is no disclosure or suggestion in Soetens of employing l-amphetamine to improve memory consolidation in a human. Further, there is no disclosure or suggestion in either Soetens or Gelowitz, taken either separately or in combination, of a method of improving memory consolidation in a human by administering l-amphetamine. Soetens, which teaches an improvement in memory consolidation with d-amphetamine, when combined with Gelowitz which teaches, as discussed *supra*, that the cognitive enhancing ability of l-deprenyl is matched by the cognitive enhancing ability of l-amphetamine, which is considerably less active than d-amphetamine, do not teach a method of improving memory consolidation by administering l-amphetamine, which is the subject matter of Applicants' claimed invention. Therefore, neither Soetens nor Gelowitz, taken either separately or in combination, disclose or suggest Applicants' claimed invention.

Brown describes improvement in the Morris Water Task performance in rats following the posttraining administration of d-amphetamine. Brown also describes the elimination of the facilitory effects of posttraining d-amphetamine by the administration of eticlopride, a dopamine 2 (D2) antagonist.

As with Gelowitz and Soetens, there is no disclosure or suggestion in Brown of Applicants' claimed method of improving memory consolidation in a human by administering l-amphetamine as set forth in Claims 91-115 and 117-119. Brown does not remedy the deficiencies of Gelowitz, alone or in combination, with Soetens. Specifically, the results described by Brown improve memory following the administration of d-amphetamine and the methods employed by Brown are not used to treat humans. Further, there is no teaching or suggestion in Brown of using l-amphetamine in rats under similar experimental conditions described by Brown nor in humans having to improve memory consolidation.

The combination of Gelowitz, Soetens and Brown is an improper combination of references under the Patent Law. As stated in Section 2141 of the MPEP (*supra*), the references themselves must suggest the combination and, in this case, the references cited by the Examiner, do not suggest Applicants' claimed invention.

As discussed above, Gelowitz does not specifically teach memory consolidation, does not mention memory consolidation and the modified Morris Water Maze test employed by Gelowitz does not assess memory consolidation. Further, the purpose of Gelowitz is to compare the effects of l-deprenyl and l-amphetamine on brain monoamine oxidase activity and cognitive performance (acquisition of learned spatial memory) of middle aged rats. In addition, Gelowitz expressly teaches that l-amphetamine is considerably less active than d-amphetamine. As also discussed above, the teachings of Soetens relate specifically to improving memory consolidation in humans by administering d-amphetamine and lack any teaching relating to the use of l-amphetamine. Absent impermissible hindsight reconstruction of Applicants' claimed invention, as amended, one of ordinary skill in the art would not combine Gelowitz which does not specifically assess memory consolidation, describes testing of the effect of l-amphetamine on a different cognitive component and expressly teaches that l-amphetamine is considerably less active than d-amphetamine, with Soetens which only teaches the effects of d-amphetamine on memory consolidation.

Similarly, there is nothing in Brown, which teaches improvements in the Water Maze Task performance of rats following posttraining administration of d-amphetamine, which would suggest its combination with Gelowitz and/or Soetens. The suggestion required by the Patent

Law (e.g., Section 2141 of the MPEP) in the references themselves for a proper combination of references is absent in Gelowitz, Soetens and Brown, alone or any combination.

Even when Gelowitz, Soetens and Brown are combined, using impermissible hindsight, the combined teachings do not teach or suggest Applicants' claimed invention. For example, combining the teachings of Gelowitz and Soetens produces the combined teaching that the learned spatial memory effect of l-deprenyl is matched by that of l-amphetamine, but l-amphetamine is considerably less active than d-amphetamine (Gelowitz) and d-amphetamine improves memory consolidation in humans (Soetens). The combined teachings are not Applicants' claimed invention, as amended, and do not suggest Applicants' claimed invention. A similar failure to teach or suggest Applicants' claimed invention, as amended, results when the teachings of Brown are combined with the teachings of Gelowitz or Soetens, alone or together, as discussed above. Thus, the combination of Gelowitz, Soetens and Brown is an improper combination and does not, either alone or in combination, render Applicants' claimed invention, as amended, *prima facie* obvious. In addition, objective evidence further supports the nonobviousness of Applicants' claimed invention.

Objective evidence of nonobviousness must be considered, as stated in Section 2141 of the MPEP:

Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

The data described in the instant application show that one of ordinary skill in the art would not have expected the results obtained by Applicants' claimed method as described, for example, in Figures 1, 8 and 13-15 and on pages 90-97. As shown in Figures 1 and 8, treatment of rats with d-amphetamine or l-amphetamine, respectively, improved memory consolidation as evaluated in the Inhibitory Avoidance Task, a well recognized behavioral paradigm to assess consolidation of memory. As shown in Figure 1, a 2.0 mg/kg of d-amphetamine resulted in a

retention time less than the retention time achieved with one-fourth ($\frac{1}{4}$) the dose of l-amphetamine (0.5 mg/kg, as shown in Figure 8). Further, l-amphetamine (Figure 14) produced minimal or no side effects compared to d-amphetamine (Figure 15). Moreover, as shown in Figure 13, l-amphetamine improved the discrimination index observed in fornix lesioned rats, a well recognized model for an impairment in memory consolidation. Discrimination index was assessed using the Spontaneous Object Recognition Task, also a well recognized behavioral paradigm to assess memory consolidation.

In addition, Dr. Carpenter states in his Declaration that additional data, obtained subsequent to the filing of the instant application, confirm generally equal efficacy of l-amphetamine and d-amphetamine in improving memory consolidation in rats when l-amphetamine is administered to the rats at about one-half ($\frac{1}{2}$) and about one-fourth ($\frac{1}{4}$) the dose of d-amphetamine. One of ordinary skill in the art would not have expected these results from the teachings of the prior art.

The teachings of the art would not have lead a person of ordinary skill in the art to expect the results observed employing l-amphetamine. As noted above, Gelowitz teaches that l-amphetamine is “considerably less active” than d-amphetamine (*supra*). In addition, Nickel, *et al.*, *Neuropharmacology* 29:983-992 (1990) (hereinafter “Nickel”), cited in an Information Disclosure Statement, filed on November 1, 2002, as reference AN, states on page 990:

The central [nervous system] action of (-)-amphetamine [l-amphetamine] is three or four times less than that of (+)-amphetamine [d-amphetamine].

The teachings of the art, including Gelowitz and Nickel, would have expected the effects of l-amphetamine to be “considerably less” (Gelowitz, *supra*), likely “three or four times less” effective (Nickel, *supra*) than d-amphetamine. However, as shown in the instant application, the effects of l-amphetamine were unexpectedly as effective as d-amphetamine at one-fourth ($\frac{1}{4}$) the dose of d-amphetamine (see, for example, Figures 1 and 8 of the instant application).

Furthermore, Gelowitz and Soetens were published in 1994 and 1993; yet, to date, 2003, other than Applicants’ claimed invention, there are no treatments employing l-amphetamine to treat impairments in memory consolidation in humans. Moreover, as Dr. Carpenter states in his

Declaration, impairments in memory consolidation in humans are a prevalent health issue for which there are no currently available clinically efficacious treatments, except Applicants' claimed invention which has been and is being used in human clinical trials. Therefore, objective evidence including unexpected results, long-felt need and failure of others are relevant and support the nonobviousness of Applicants' claimed invention.

In addition, Dr. Carpenter in his Declaration states that Gelowitz, Soetens and Brown do not teach or suggest, either alone or in combination, Applicants' claimed invention. Dr. Carpenter further states that the teachings of those skilled in the art, including Gelowitz and Nickel, would not have predicted the unexpected results achieved. He also describes results from Phase I human clinical trials, performed by Sention, Inc., which show the effect of Applicants' claimed invention. Dr. Carpenter further states in his Declaration that treatment of humans in Phase I clinical trials with l-amphetamine produces unexpected results that one of ordinary skill in the art would not expect from the use of l-amphetamine, as taught by Gelowitz, Soetens and Brown, taken either separately or in combination.

Specifically, there is no disclosure or suggestion in Gelowitz, taken either separately or in combination with Soetens or Brown, of a method of improving memory consolidation in a human by administering l-amphetamine. In addition, as evidenced by the enclosed Declaration by Dr. Carpenter, Applicants have demonstrated unexpected results that one of ordinary skill in the art would not predict in view of the teachings of Gelowitz, Soetens and Brown, taken separately or in combination. Further, additional evidence of the nonobviousness of the instant invention include the failure of others and a long-felt need to develop a safe and effective method of improving memory consolidation in humans, which is the subject matter of Applicants' claimed invention.

SUMMARY AND CONCLUSIONS

The subject matter of amended Claims 91-115 and 117-119 would not have been obvious to one of ordinary skill in the art under 35 U.S.C. § 103(a) in view of Gelowitz, Soetens and Brown, taken either separately or in combination. Thus, Claims 91-115 and 117-119 meet the requirements of 35 U.S.C. § 103(a). Therefore, Applicants respectfully request reconsideration and allowance of these claims.

If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call Applicants' undersigned Attorney.

Respectfully submitted,
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